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[Diagnostic Test Accuracy Protocol]

Contrast-enhanced ultrasound compared with computed tomography, magnetic resonance imaging, and positron emission tomography-computed tomography for diagnosing liver metastases in people with newly diagnosed colorectal cancer

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (diagnostic). The objectives are as follows:

To determine the diagnostic accuracy of contrast-enhanced ultrasound (CEUS) versus contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), and fluro-18-deoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT) for diagnosing liver metastases in people with newly diagnosed colorectal cancer.
ZZZ <section xml:id="CD012388-abs2-0001"> ZZZ
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We plan to investigate the following potential sources of heterogeneity.

- Study design (prospective compared to retrospective)
- Study date (studies conducted before the year 2000 compared to studies conducted after the year 2000) due to advancements in technology and change in diagnostic criteria
- Participant selection (participants recruited from planned screening programmes compared to clinical setting)
- Proportion of participants with resectable liver metastasis
- Maximum diameter of the largest liver lesion
- Differences in operator skills in CEUS performance, assessed by years of experience
- Different reference standards (studies using pathology of resected liver compared to studies using histology of hepatic lesion)

BACKGROUND

Colorectal cancer (CRC) is one of the most common cancers in the Western world. In general, it ranks third in terms of incidence, and second in terms of mortality (Bray 2018). Incidence rates are significantly higher in high-income countries; however, the average case fatality is higher in middle-income and low-income countries (Bray 2018; Fitzmaurice 2018). Globally, the probability of developing colorectal cancer is higher in men than women (1 in 26 men; 1 in 41 women) (Fitzmaurice 2018). From the time of diagnosis, the five-year relative survival rate in the USA, adjusted for normal life expectancy, is 65% (Siegel 2019).

Since the mid-1980s, there has been a decline in incidence of colorectal cancer in the USA. Between 2008 and 2011, the decline has been 4% or larger per year. This decline is most likely due to increased uptake of screening, primarily in the form of colonoscopy. During colonoscopy, precancerous legions can be removed to help prevent cancer development (Siegel 2019). In the USA, the use of colonoscopies among adults aged 50 years and older increased from 21% in 2000 to 60% in 2015 (Siegel 2019).

Metastatic liver disease is a very common clinical situation in oncology. In context of colorectal cancer, the liver is the most common site of metastatic spread. Liver metastases may be synchronous (i.e. diagnosed at the same time as the primary tumour), or metachronous (i.e. develop during follow-up after surgical resection of the primary tumour). Surgical resection, stereotactic radiation therapy, and radiofrequency ablation represent curative therapy options in people with colorectal cancer who have a limited number of metastatic lesions (Cirocchi 2012). However, it is a clinical challenge to diagnose and localise liver metastases at an early stage, when curative treatment options can still be beneficial.

Around 20% to 25% of all people with colorectal cancer have metastatic spread at the time of diagnosis, and approximately 50% of all these people develop liver metastases during the course of colorectal cancer (Kanas 2012; Vatandoust 2015). Metastases confined to the liver at the time of colorectal cancer detection are potentially resectable in 10% to 30% of patients (Kanas 2012; Vatandoust 2015). Hepatic resection is considered to be the best curative treatment for liver-limited colorectal cancer metastases. However, there are some contraindications to hepatic resection, which include unresectable extrahepatic disease, more than 70% of liver involvement, liver failure, and being surgically unfit (Vatandoust 2015). The lungs are the second most common site of distant metastases in people with colorectal cancer, and the peritoneum is the third (Vatandoust 2015). In people with isolated hepatic lesions, five-year survival after surgical resection is reported to range from 16% to 74% (median 38%) (Kanas 2012); other studies report five-year survival ranging from 25% to 58%, and 10-year survival is reported to range from 17% to 28% (Vatandoust 2015). It is therefore important to detect and treat colorectal cancer liver metastases as early as possible in order to offer patients the best possible treatment. The first step in this process is a reliable triage test to detect liver metastases. The next step is to identify patients who may be candidates for surgery, and this highly depends on diagnostic imaging. In order to determine resectability, it is crucial that diagnostic imaging modalities can demonstrate the exact number, size, regional distribution, and volume of the remaining liver tissue.

A number of diagnostic systematic reviews exist which assess various imaging modalities for the detection of liver metastases, including ultrasound, contrast-enhanced ultrasound (CEUS), computed tomography (CT), magnetic resonance (MR), fluro-18-deoxyglucose positron emission tomography (FDG PET), and fluro-18-deoxyglucose positron emission tomography/computed tomography (18-F-FDG PET/CT) (Kinkel 2002; Bipat 2005; Floriani 2010; Niekel 2010; Chen 2012; van Kessel 2012; Westwood 2013; Maffione 2015; Vilgrain 2016; Vreugdenburg 2016; Choi 2018). These reviews included primary studies which assessed the diagnostic accuracy of a single index test, as well as studies which compared different imaging modalities. They showed highly variable diagnostic accuracy, ranging from 52% to 93% for sensitivity and from 10% to 94% for specificity. The reviews used mixed datasets, including data on people who developed liver metastases from colorectal cancer, other origins, or both. Other reviews included people treated with neoadjuvant chemotherapy (Floriani 2010; van Kessel 2012; Maffione 2015; Vilgrain 2016; Choi 2018), in which the diagnostic performance of imaging might be affected due to sinusoidal obstruction syndrome, induced steatosis, or pseudocirrhosis (Sharma 2014). People treated with neoadjuvant chemotherapy and people with non-colorectal liver metastases are not the target population of our review. Apart from the meta-analysis by Westwood and colleagues, none of the meta-analyses assessed the accuracy of CEUS and its role in the diagnostic pathway of colorectal cancer liver metastases. A Cochrane Review is currently in progress, which has the primary objective of determining the diagnostic accuracy of integrated 18F-FDG PET/CT as a replacement test for conventional imaging for preoperative staging of recurrent colorectal cancer (Crawford 2012).

Due to the growing volume of scientific literature and insufficient evidence documented in reviews, we aim to assess the diagnostic accuracy of CEUS compared with other imaging modalities for the detection of colorectal cancer liver metastases in people with newly diagnosed colorectal cancer. We aim to systematically review and assess the role of CEUS in the diagnostic pathway compared with other imaging modalities, and to assess the accuracy of all modalities in the detection of colorectal cancer liver metastases in people with newly diagnosed colorectal cancer.

Target condition being diagnosed

The clinical target condition of this review is colorectal cancer liver metastases in people with newly diagnosed colorectal cancer.

Index test(s)

Contrast-enhanced ultrasound (CEUS)

An ultrasound scanner is a medical imaging modality which uses echoes from ultrasound waves to produce live images of anatomical structures. The ultrasound transducer is handheld and is placed directly on the skin in the anatomical area of interest. CEUSuses plain ultrasound scanners with the addition of an ultrasound contrast agent. The contrast agent is administered as an intravenous bolus which allows the study of liver perfusion in real time. Due to the use of the contrast agents, it is possible to characterise focal liver lesions with patterns of enhancement. The contrast agent consists of microbubbles (sulphur hexafluoride) and serious adverse effects are unknown (Solbiati 2003). The advantage of CEUS is lack of ionising radiation, consequently with no harm to the human body (Solbiati 2003). It is a relatively fast examination

that can be performed in approximately 30 minutes. If necessary, it is possible to perform a biopsy of suspected lesions in the liver during the examination. The disadvantage is that the value of CEUS depends on the skills of the physician performing the examination (Solbiati 2003). Even with the possibility to store images, there is no guarantee that other physicians will be able to interpret them. Ultrasound scanners are affordable and widely available in clinical centres in most countries.

Contrast-enhanced computed tomography (CECT)

A CT scanner is a medical imaging modality based on x-rays. Images are acquired while the person is moving through a circle-shaped gantry, in which the x-ray tube and the chain of detectors are circling at high speed. A contrast agent is administered as an intravenous infusion by an automatic syringe CT injector to visualise the perfusion of the inner organs**.** The advantages of CECT are the short examination time (lasting from 5 minutes to 15 minutes), and the immediate availability of images for interpretation. CECT may also be used to examine extra-hepatic tissues and organs. Similarly to CEUS, it is possible to characterise focal liver lesions with patterns of enhancement. The images are stored electronically and are available to other physicians. CT volumetry allows volume estimation of the future liver remnant in the case of hepatic resection (Lim 2014). Disadvantages of CECT arise from relatively high doses of ionising radiation and the use of iodine-based contrast agents, which are known to cause certain high-risk adverse effects such as allergic reactions and anaphylactic shock. Therefore, one of the contraindications for referring patients for CECT is previous allergic reactions to iodine-based contrast agents. Another contraindication is renal insufficiency, due to the increased risk of kidney failure. CT scanners are widely available in clinical centres in many countries, even though their price is relatively high (NCHS 2011).

Magnetic resonance imaging (MRI)

A MRI scanner is a medical imaging modality which uses a strong magnetic field and radio waves to produce images of the body. The magnet is in the form of a large tube, in which a person is positioned. The basic types of MRI images are called T1 and T2. The timing of radiofrequency pulse sequences determines if the images are T1-weighted highlighting fat, or T2-weighted highlighting fat and water within the body. The advantages of MRI are similar to CEUS; it is performed without the use of ionising radiation, with no harm to the human body (Westbrook 2011). Based on chemical compound, two important types of intravenously-administered contrast agents exist: gadolinium-based and ferucarbotran-based (superparamagnetic iron oxide). According to their distribution in the body, contrasts are divided into extracellular and hepatobiliary agents. The latter allow additional focal liver lesion characterisation in hepatobiliary phase (Agnello 2016). These contrast agents are not known to have serious adverse effects if they are used in small doses. However, people with renal insufficiency are known to be at high risk of adverse effects such as developing nephrogenic systemic fibrosis, especially if the gadolinium agents are used in high doses. Another disadvantage is that MRI is a time-consuming examination compared to CEUS and CECT. It takes approximately one hour to perform a MRI scan of the liver. Contraindications for MRI examination are claustrophobia and ferromagnetic metal implants. However, people with claustrophobia are often able to complete a MRI examination in an open MRI scanner. MRI scanners are widely available in clinical centres in the western world, but many countries in other parts of the world do not have extensive access to MRI scanners (NCHS 2011). MRI scanners are very expensive and they need a very powerful source of electricity.

Fluro-18-deoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT)

A PET/CT scanner is a medical imaging modality based on x-rays and the use of a gamma camera. It includes an ordinary CT scanner and a gamma camera, a device used to produce images obtained by means of gamma radiation-emitting radio-isotopes, administered as an intravenous infusion. The advantage of 18F-FDG PET/CT is that it provides information on glucose uptake and therefore metabolism of malignant cells in the liver, as well as anatomic alterations such as visible liver lesions (Czernin 2010). The disadvantages are the same as for CECT concerning the ionising radiation; however, there is no use of iodine-based contrast agents. Patients are given an intravenous infusion of fluro-18-deoxyglucose (18F-FDG) with an effective dose of approximately 6 to 7 millisievert (mSv). 18F-FDG PET/CT is a time-consuming examination: a full scan lasts approximately three hours. It has been suggested that hyperglycaemia and diabetes can affect the diagnostic value of 18F-FDG PET/CT, because the cellular uptake of 18F-FDG is adversely affected by elevated plasma glucose levels (Rabkin 2010; Mirpour 2012). However, there was no significant difference in diagnostic accuracy between diabetic and non-diabetic patients, and therefore high serum glucose is now no longer considered a contraindication for an 18F-FDG PET/CT exam (Rabkin 2010; Mirpour 2012). PET/CT scanners are widely available in main clinical centres in the western world, but many countries in other parts of the world do not have access to PET/CT scanners due to their high cost.

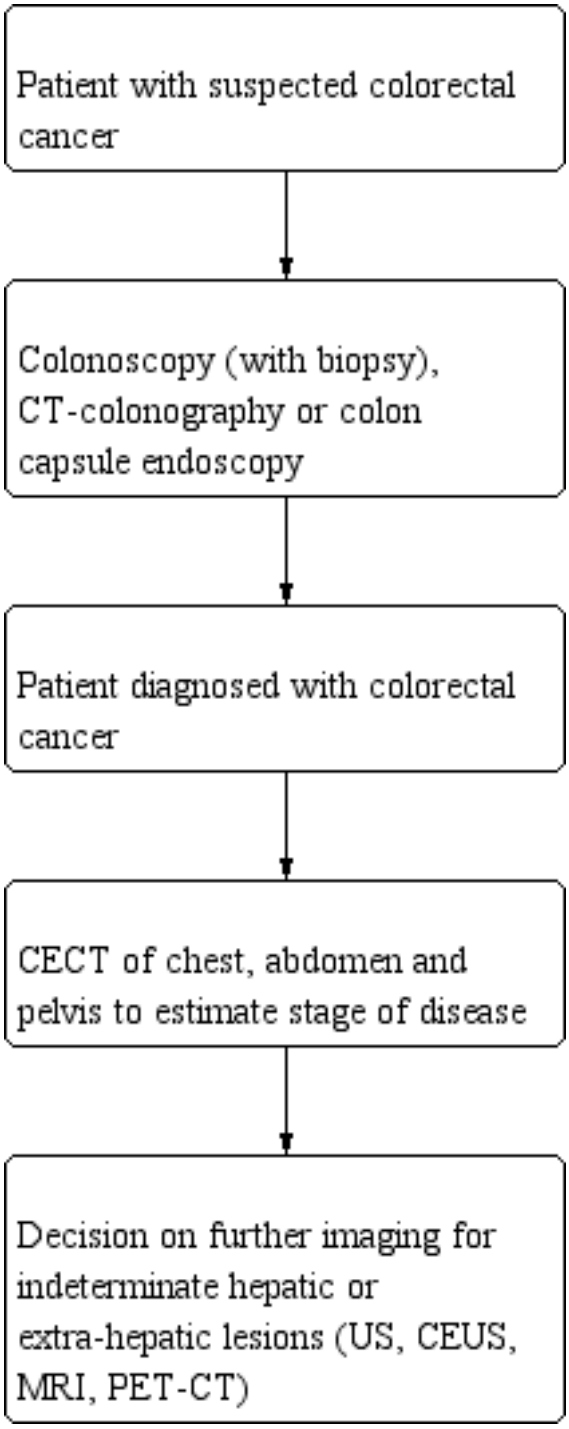
Clinical pathway

According to current guidelines from relevant societies worldwide, CECT is proposed as the standard imaging modality in staging of newly diagnosed colorectal cancer as well as initial detection of liver metastasis (NICE 2014; Van Cutsem 2016; Vogel 2017; Yoshino 2018; NCCN 2020). CECT is a very fast and reliable examination, and the images are easily shared among clinicians who have an interest in the examination. CT images can be processed in different ways, which makes it possible to assess liver lesions from different angles and in both two and three dimensions. This also makes CECT a very important tool for surgeons assessing the possibilities of hepatic resection.

The above-mentioned guidelines vary or give general information on the proposed imaging modalities after the initial CECT, or in patients where CECT is contraindicated. According to guidelines from the National Insitute for Health and Care Excellence (NICE), a multidisciplinary team should decide whether further imaging is required (NICE 2014). European Society for Medical Oncology (ESMO) and Pan-Asian adapted ESMO consensus guidelines recommend performing US, CEUS, or MRI in case of indeterminate liver lesions on CECT (Van Cutsem 2016; Yoshino 2018). The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines and National Comprehensive Cancer Network (NCCN) guidelines recommend using non-contrast enhanced chest CT and MRI of the abdomen and pelvis in case of hypersensitivity to iodine (Vogel 2017; NCCN 2020). 18F-FDG PET/CT is generally

recommended for evaluation of suspected extrahepatic lesions (Figure 1).

Figure 1. Clinical pathway.



Magnetic resonance imaging and 18F-FDG PET/CT are generally used as additional imaging modalities after CECT or when CECT is contraindicated. Concerning the role of CEUS in the diagnostic pathway, only ESMO and Pan-Asian guidelines state that CEUS might have a role in additional characterisation of suspected liver metastasis (Vogel 2018; Vogel 2019; Yoshino 2018). Other guidelines do not include CEUS in the diagnostic pathway.

Prior test(s)

Prior to the imaging examinations, colorectal cancer has been detected by non-invasive fecal tests like the guaiac fecal occult

blood test (gFOBT) or the fecal immunochemical test for haemoglobin (FIT), with or without colonoscopy. People presenting with haematochezia, weight loss, night sweats, and iron deficiency anaemia have clinical symptoms of colorectal cancer. The primary diagnostic tool for these people is colonoscopy. The differential diagnoses are haemorrhoids, anal fissure, diverticular disease, colitis, inflammatory bowel disease, or angiodysplasia. Differential diagnoses may also include upper gastrointestinal bleeding caused by varicose veins of the oesophagus, tears in the oesophagus, or peptic ulcers in the lining of the stomach or duodenum. The gFOBT and the FIT are often used as the primary screening test in colorectal cancer screening programmes. In case of a positive fecal test for blood, colonoscopy will be offered as the secondary screening test. Colonoscopy is an invasive imaging technique and is the reference standard to detect colorectal cancer and its precursor lesions. Colonoscopy is therefore used as the primary screening tool in some colorectal cancer screening programmes (Schreuders 2015).

Role of index test(s)

This review will assess the diagnostic accuracy of four index tests: CEUS, CECT, MRI, and 18F-FDG PET/CT, with emphasis on CEUS. According to guidelines and clinical practice, all of these tests, except CEUS, have a role in the diagnostic pathway. We want to focus on the accuracy of CEUS compared with other imaging modalities in order to determine its potential role in the diagnostic pathway as a replacement or as an add-on test (Bossuyt 2006).

Colorectal cancer may metastasise to other parts of the body than the liver, and CECT can examine hepatic tissue as well as other organs at the same time. For this reason, CECT is a better choice for staging than CEUS because the diagnostic value of CEUS is restricted to the liver. CEUS could be a replacement or an add-on test in the existing pathway, depending on the accuracy compared with MRI and 18F-FDG PET/CT. The potential role of CEUS as a second- or third-line test is beneficial, as it does not expose the person to high doses of radiation or iodine, or to gadolinium-based contrast agents.

Rationale

The detection and diagnosis of colorectal cancer liver metastases in people with newly diagnosed colorectal cancer is important for the staging of the disease. Furthermore, it is important to detect the exact number of liver metastases, their size, their regional distribution, and the volume of the remaining liver in order to determine resectability. The first step in the diagnosis is to determine whether liver or extra-hepatic metastases (or both) are present. CECT is the modality of choice in current clinical pathways as a triage test for the detection of liver and extra-hepatic colorectal cancer metastases. MRI and 18F-FDG PET/CT are second-line options in case of indeterminate liver lesions detected on CECT. CEUS does not have a clear role in the diagnostic pathway, apart from having a potential benefit in characterising suspected liver lesions that are equivocal on the initial CECT. We want to explore the use of CEUS concerning the detection of liver metastases, and in the characterisation of equivocal lesions on CECT. CEUS could be a replacement test instead of MRI or PET/CT for liver lesions. We want to explore the effectiveness of CEUS in the assessment of the exact number of liver metastases, their size, regional distribution, and volume of the remaining liver, to determine resectability.

This review aims to assess and compare the accuracy of CEUS with other imaging modalities, and to determine its role in the current diagnostic pathway for the diagnosis of liver metastases in people with newly diagnosed colorectal cancer.

OBJECTIVES

To determine the diagnostic accuracy of contrast-enhanced ultrasound (CEUS) versus contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), and fluro-18-deoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT) for diagnosing liver metastases in people with newly diagnosed colorectal cancer.

Secondary objectives

We plan to investigate the following potential sources of heterogeneity.

- Study design (prospective compared to retrospective)
- Study date (studies conducted before the year 2000 compared to studies conducted after the year 2000) due to advancements in technology and change in diagnostic criteria
- Participant selection (participants recruited from planned screening programmes compared to clinical setting)
- Proportion of participants with resectable liver metastasis
- Maximum diameter of the largest liver lesion
- Differences in operator skills in CEUS performance, assessed by years of experience
- Different reference standards (studies using pathology of resected liver compared to studies using histology of hepatic lesion)

METHODS

Criteria for considering studies for this review

Types of studies

We plan to include cross-sectional studies that assess the diagnostic accuracy of CEUS for the diagnosis of liver metastases in people with newly diagnosed colorectal cancer. We will include both non-comparative studies (CEUS against the reference standard) and comparative studies comparing the index test (CEUS) and one or more comparators (CECT, MRI, or 18F-FDG PET/CT) in the same study population, either by giving all participants the index test or by randomly allocating participants to receive the index test or one comparator against the same reference standard.
We will include studies irrespective of language or publication status, or whether data were collected prospectively or retrospectively. We will include studies presenting data on a per-patient basis and exclude studies presenting data on a per-lesion basis.

Participants

The study population will include adults aged 18 years or older with newly diagnosed colorectal cancer. We will not include people with known liver metastases and people who have already undergone hepatic resection or local treatment. We will exclude studies which assess the diagnostic accuracy of index tests in the detection of liver metastases from other origins, unless data are presented in a way which allows the population with colorectal cancer to be analysed separately.

Index tests

The index test is CEUS and the comparators are CECT, MRI, and 18F-FDG PET/CT.

The characteristic feature of a liver metastasis on CEUS is a reduced contrast uptake in the portal venous phase and in the late phase, consequently giving the appearance of a hypoechoic lesion. In the arterial phase, liver metastasis can present as a hypervascular or hypovascular lesion. In the case of a hypervascular metastasis, the lesion presents with increased contrast uptake, giving it a hyperechoic aspect. A hypovascular metastasis will be hypoechoic, usually with a peripheral enhancement (Cantisani 2014; D'Onofrio 2015).

On non-contrast CT, a liver metastasis is usually a low- or isoattenuated mass, when compared with the surrounding normal tissue. In the arterial phase, a hypervascular metastasis shows diffuse enhancement, while a hypovascular metastasis shows peripheral ring enhancement. In portal and venous phases, metastatic lesions show a "washout" phenomenon, a characteristic malignant feature, and a thick ring enhancement (Sica 2000; Lincke 2017).

Regarding MRI, although most metastases are hypo- to isointense on T1 and iso- to hyperintense on T2-weighted images, typical hallmarks of liver metastases are peripheral ring enhancement, diffusion restriction, and hypointensity on hepatobiliary phase images (Namasivaya 2007; Karaosmanoglu 2016).

On PET imaging, a liver lesion is considered malignant when it demonstrates an area of focally increased FDG uptake, i.e. greater intensity than surrounding normal hepatic tissue uptake. A diagnosis of metastasis can be made by combining the malignant PET feature with malignant CT features (Rachh 2014).

Target conditions

The target condition is colorectal cancer liver metastases in people with newly diagnosed colorectal cancer.

Reference standards

We will accept a reference standard for the diagnosis of liver metastases as one of the following.

- In case of surgical resection, the pathology of the resected lesion
- In case of unresectable liver lesions, biopsy and histology of suspected liver lesions with follow-up of at least three months to exclude any synchronous lesions not detected by the index test(s)
- In case of negative results on index test(s), a follow-up with imaging for at least three months to confirm initial negative results.

None of the above-mentioned reference standards are perfect. In case the reference standard is the pathology of the resected liver specimens, people with negative results of index test(s) do not undergo surgery and require an appropriate follow-up. The same applies for people who undergo biopsy: those with initial negative index test(s) are not eligible to undergo biopsy. Therefore, a follow-up with imaging is necessary. Ideally, the same imaging modality should be used for follow-up as the initial evaluation. It is not possible that all participants undergo the same reference standard, introducing an unavoidable differential verification bias. However, we find it necessary that all participants in the same category (people with resectable liver metastases, people with non-resectable liver metastases, and people with negative index test(s)) are evaluated by the same reference standard.

Search methods for identification of studies

Electronic searches

We will conduct electronic searches in the Cochrane Hepato-Biliary Group Controlled Trials Register and the Cochrane Hepato-Biliary Group Diagnostic Test of Accuracy Studies Register (both are maintained and searched internally by the CHBG Information Specialist via the Cochrane Register of Studies Web), the Cochrane Library, MEDLINE Ovid, Embase Ovid, LILACS (Bireme), Science Citation Index Expanded (Web of Science), and Conference Proceedings Citation Index – Science (Web of Science) (Royle 2003; De Vet 2008). We will apply no language or document type restrictions. The time spans will be published for each of the separate databases at review stage. See Appendix 1 for preliminary search strategies.

Searching other resources

We will try to identify additional references by manually searching articles retrieved from digital databases and relevant review articles. We will seek information on unpublished studies by contacting experts in the field. In addition, we will handsearch abstract books from meetings over the past 10 years of the European Society for Medical Oncology (ESMO), The American Society of Colon and Rectal Surgeons and National Comprehensive Cancer Network (NCCN). We will also search for other kinds of grey literature in the System for Information on Grey Literature in Europe “OpenGrey” (www.opengrey.eu/).

Data collection and analysis

We will follow the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* (De Vet 2008; Deeks 2013; Reitsma 2013).

Selection of studies

We will use Covidence to manage the selection of studies (Covidence 2017). Two review authors (ML and TAB) will independently scrutinise titles and abstracts identified by electronic literature searching to identify potentially eligible studies. Any citation that is identified by either review author as potentially eligible will be selected for full-text review. The same review authors will independently assess full-text papers for study eligibility, using predefined inclusion and exclusion criteria. We will resolve any discrepancies by discussion. We will record all studies after full-text assessment, and their reasons for exclusion, in the 'Characteristics of excluded studies' table and illustrate the study selection process using a PRISMA diagram (Moher 2009).

Data extraction and management

Two review authors (ML and TAB) will independently complete a data extraction form for all included studies and retrieve the following data.

- General information: title, journal, year, publication status, and study design

- Surveillance programme or clinical cohorts
- Sample size: number of participants meeting the criteria and total number of participants screened
- Baseline characteristics: baseline diagnosis, age, sex, ethnicity
- Index tests with predefined positivity criteria and target condition
- Order of tests
- Time between tests
- Reference standard tests
- Numbers of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) findings. We will extract these data for liver metastasis of any size, number, and resectability.

We will summarise the data from each study in 2 x 2 tables (TP, FP, FN, TN), according to the index tests considered, and we will enter the data into Review Manager 5.3 software (Review Manager 2014).

Missing data

We will contact primary authors by email to ask for missing data which are needed to design the 2 × 2 tables. If we receive no reply, we will send a second email after two weeks. If no reply is received, we will exclude the study in question.

Assessment of methodological quality

Two review authors (ML and TAB) will use QUADAS-2 for the assessment of the methodological quality of the studies (Whiting 2011; Appendix 2). The QUADAS-2 items have been incorporated into Review Manager 5 (Review Manager 2014). Appendix 2 contains definitions on when to answer yes, no, or unclear to the signalling questions within the QUADAS-2 items, as well as definitions on when the risk of bias should be considered high, low, or unclear (Appendix 2). We will classify a study as having a high risk of bias if at least one of the domains of QUADAS-2 is judged as being high risk. We will resolve any disagreements between the two review authors concerning the methodological quality of the studies by consensus. In case of disagreement, a third author (the arbiter) will make the final decision.

Statistical analysis and data synthesis

We will present each index test in each study as binary data in a 2 x 2 table. The test results from the studies have to be reported as true positive (TP), true negative (TN), false positive (FP), or false negative (FN). We will tabulate and graphically present these values from the selected studies in coupled forest plots (including 95% confidence intervals (CIs)). We will also estimate the positive and negative predictive values, and the positive and negative likelihood ratios (LR+ and LR-), with 95% CIs. Furthermore, we will plot the results on a receiver operating characteristic diagram (ROC, sensitivity against 1 - specificity). We will present each of the four index tests in their own ROC space, with the data available from each study. Since we expect a common implicit cut-off among studies, we will use the bivariate model to pool sensitivities and specificities and to estimate the summary operating point (i.e. mean sensitivity and specificity) for each index test. We will perform direct and indirect comparisons by adding the four index tests as covariates to the bivariate model (Reitsma 2005). We will assess the significance of differences in test accuracy by using the log-likelihood ratio test for comparison of models with and without the index test covariate term. We will consider P values less than 0.05, two-sided, as statistically significant. We will conduct all analyses and plots using Review Manager 5 (Review Manager 2014) and SAS software (SAS software 2008).

In case of non-evaluable index test results (especially relevant for CEUS), we plan to analyse data according to the intention-to-diagnose (ITD) principle (Schuetz 2012). We will classify participants with non-evaluable results as false positive if they had a negative reference standard, or false negative result on a positive reference standard. If data for the ITD analyses are not retrievable from the text, we will contact the study authors. If we receive no response, we will include the study in the analyses with data retrievable from the published manuscript and consider the study to be at high risk of bias.

Investigations of heterogeneity

Based on the variability in test accuracy among the studies, we plan to conduct subgroup analyses by adding covariates to the bivariate model concerning the use of different reference standards, different ways of selecting the study populations (e.g. different inclusion and exclusion criteria), different locations of the study populations (country, state, region), differences between age groups, or differences between men and women. Based on the variability in test accuracy among the studies concerning CEUS, we plan to conduct subgroup analyses by adding covariates to the bivariate model in order to investigate whether the variability is due to differences in clinician skills in the performance of CEUS. We will assess the statistical significance of each covariate term by using the log-likelihood ratio test for comparison of models with and without the covariate.

We plan to investigate the following potential sources of heterogeneity.

- Study design (prospective compared to retrospective)
- Study date (studies conducted before the year 2000 compared to studies conducted after the year 2000) due to advancements in technology and change in diagnostic criteria
- Participant selection (participants recruited from planned screening programmes compared to clinical setting)
- Proportion of participants with resectable liver metastasis
- Maximum diameter of the largest liver lesion
- Differences in operator skills in CEUS performance, assessed by years of experience
- Different reference standards (studies using pathology of resected liver compared with studies using histology of hepatic lesion)

Sensitivity analyses

We plan to assess the effects of risk of bias of included studies on diagnostic accuracy by performing a sensitivity analysis in which we will exclude studies classified as being at high risk of bias in at least one of the domains of QUADAS-2 (Appendix 2). In addition, we have defined the following signalling questions as being most relevant, and we plan to conduct a sensitivity analysis in which we will exclude studies at high risk of bias.

- "Did all participants receive the same reference standard?"
- "Were the reference standard results interpreted without knowledge of the results of the index test?"

We also plan to conduct a sensitivity analysis in which we will exclude studies published only in abstract or letter format.

Assessment of reporting bias

We do not plan to test for publication bias due to the lack of validated methods for diagnostic test accuracy reviews.

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APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy

(Continued)

The Cochrane Hepato-Biliary Group Controlled Trials Register	Date will be given at review stage	(computed tomograph* or CT or CECT or MDCT or MSCT or magnetic resonance imaging or MRI or emission tomography or PET or ultrasound or ultrasonograph* or US or CEUS) AND ((liver or hepat*) near (metasta* or secondar* or spread or advanced)) AND ((colorectal or rectal or colon) near3 (cancer or carcinom* or neoplasm* or tumor* or tumo*r))
The Cochrane Hepato-Biliary Group Diagnostic Test of Accuracy Studies Register	Date will be given at review stage	(computed tomograph* or CT or CECT or MDCT or MSCT or magnetic resonance imaging or MRI or emission tomography or PET or ultrasound or ultrasonograph* or US or CEUS) AND ((liver or hepat*) near (metasta* or secondar* or spread or advanced)) AND ((colorectal or rectal or colon) near3 (cancer or carcinom* or neoplasm* or tumor* or tumo*r))
The Cochrane Library (Wiley)	Latest issue	#1 MeSH descriptor: [Tomography, Emission-Computed] explode all trees #2 MeSH descriptor: [Tomography, X-Ray Computed] explode all trees #3 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees #4 MeSH descriptor: [Ultrasonography] explode all trees #5 (computed tomograph* or CT or CECT or MDCT or MSCT or magnetic resonance imaging or MRI or emission tomography or PET or ultrasound or ultrasonograph* or US or CEUS) #6 #1 or #2 or #3 or #4 or #5 #7 MeSH descriptor: [Liver Neoplasms] explode all trees #8 (liver or hepat*) near (metasta* or secondar* or spread or advanced) #9 #7 or #8 #10 MeSH descriptor: [Colorectal Neoplasms] explode all trees #11 (colorectal or rectal or colon) NEAR/3 (cancer or carcinom* or neoplasm* or tumo*r) #12 #10 or #11 #13 #6 and #9 and #12
MEDLINE Ovid	1946 to the date of search	1. exp Tomography, Emission-Computed/ 2. exp Tomography, X-Ray Computed/ 3. exp Magnetic Resonance Imaging/ 4. exp Ultrasonography/ 5. (computed tomograph* or CT or CECT or MDCT or MSCT or magnetic resonance imaging or MRI or emission tomography or PET or ultrasound or ultrasonograph* or US or CEUS).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 6. 1 or 2 or 3 or 4 or 5 7. exp Liver Neoplasms/ 8. ((liver or hepat*) adj (metasta* or secondar* or spread or advanced)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

(Continued)

		9. 7 or 8 10. exp Colorectal Neoplasms/ 11. ((colorectal or rectal or colon) adj3 (cancer or carcinom* or neoplasm* or tumo?r*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 12. 10 or 11 13. 6 and 9 and 12
Embase Ovid	1974 to the date of search	1. exp computer assisted tomography/ 2. exp positron emission tomography/ 3. exp nuclear magnetic resonance imaging/ 4. exp echography/ 5. exp ultrasound/ 6. (computed tomograph* or CT or CECT or MDCT or MSCT or magnetic resonance imaging or MRI or emission tomography or PET or ultrasound or ultrasonograph* or US or CEUS).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 7. 1 or 2 or 3 or 4 or 5 or 6 8. exp liver metastasis/ 9. ((liver or hepat*) adj (metasta* or secondar* or spread or advanced)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 10. 8 or 9 11. exp colorectal cancer/ 12. ((colorectal or rectal or colon) adj3 (cancer or carcinom* or neoplasm* or tumo?r*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 13. 11 or 12 14. 7 and 10 and 13
LILACS (Bireme)	1982 to the date of search	(computed tomograph$ or CT or CECT or MDCT or MSCT or magnetic resonance imaging or MRI or emission tomography or PET or ultrasound or ultrasonograph$ or US or CEUS) [Words] and ((liver or hepat$) and (metasta$ or secondar$ or spread or advanced)) [Words] and ((colorectal or rectal or colon) and (cancer or carcinom$ or neoplasm$ or tumo$)) [Words]
Science Citation Index Expanded and Conference Proceedings Citation Index – Science (Web of Science)	1900 to the date of search	#4 #3 AND #2 AND #1 #3 TS=((colorectal or rectal or colon) near/3 (cancer or carcinom* or neoplasm* or tumo?r*)) #2 TS=((liver or hepat*) near (metasta* or secondar* or spread or advanced))

(Continued)

	#1 TS=(computed tomograph* or CT or CECT or MDCT or MSCT or magnetic resonance imaging or MRI or emission tomography or PET or ultrasound or ultrasonograph* or US or CEUS)

Appendix 2. QUADAS-2 items

DOMAIN	1. PARTICIPANT SELECTION	2. INDEX TESTS	3. REFERENCE STANDARD	4. FLOW AND TIMING
Signalling questions and criteria	**Q1. Was a consecutive or random sample of participants enrolled?** Yes - if the study reports on a consecutive or a random selection of participants with newly diagnosed colorectal cancer No - if the study reports on another form of selection of participants Unclear - if the study does not report on how the participants were enrolled	**Q1. Were the index test results interpreted without knowledge of the results of the reference standard?** **For all index tests (CEUS, CT, MRI, PET/CT):** Yes - if the study reports that the results of the index test were interpreted without the knowledge of the results of the reference standard No - if the study reports that results of the index test were interpreted with the results of the reference standard Unclear - if the study provides no information on blinding of the results of the index test and reference standard	**Q1. Is the reference standard likely to correctly classify the target condition?** Yes - if the reference standard correctly defines the presence/absence of liver metastasis (e.g. pathology of surgically resected liver lesion) No - if other reference standards are used apart from those defined by this study (see Reference standards) Unclear - if the study does not report on the reference standard used	**Q1. Was there an appropriate interval between index test(s) and reference standard?** Yes - if the interval between the index test and the reference standard was less than 3 months No - if the interval was longer than 3 months Unclear - if the study does not report the interval between the index test and the reference standard
	Q2. Was a case-control design avoided? Yes - if case-control design was avoided No - if the study was case control Unclear - if the study design is not clear	**Q2. Were positivity criteria clearly defined?** **For all index tests (CEUS, CT, MRI, PET/CT):** Yes - if the study clearly reports positivity criteria for the index test(s) in question (see "Index tests") No - if the study does not report positivity criteria	**Q2. Were the reference standard results interpreted without knowledge of the results of the index test?** Yes - if the study reports that the results of the reference standard were interpreted without the knowledge of the results of the index test No - if the study reports that the results of the reference standard were interpreted with	**Q2. Did all participants receive the same reference standard?** Yes - if the study has only one reference standard for all the participants No - if the study has more than one reference standard Unclear - if the study information regarding the use of reference standard is unclear
	Q3. Did the study avoid inappropriate exclusions? Yes - if study exclusion criteria are properly defined (e.g. participants with previously treat-			**Q3. Were all participants included in the analysis?** Yes - if all enrolled participants were included in the analysis

(Continued)

	ed liver metastasis, or participants with recurrent CRC) No - if exclusion criteria are inappropriate and exclusions are not reported Unclear - if the study does not report causes of exclusions		the knowledge of the results of the index test Unclear - if the study does not report information about blinding of the results of the reference standard and the index test	No - if any participant was excluded from the analysis for any reason or non-evaluable index test results were not analysed according to intention to diagnose principle Unclear - if the exclusion of participants from the analysis is unclear
				Q4: Were participants with a non-evaluable result of the index test included and analysed according to intention to diagnose principle (non-evaluable results considered as false)? Yes - if all participants with non-evaluable results of index test were included and considered as false No - if participants with non-evaluable results of index test were not considered as false, and not included in the analysis
Risk of bias	**Could the selection of participants have introduced bias?** Low risk: "yes" for all signalling questions High risk: "no" or "unclear" for at least one signalling question	**Could the conduct or interpretation of the index test have introduced bias?** Low risk: "yes" for all signalling questions High risk: "no" or "unclear" for at least one signalling question	**Could the reference standard, its conduct, or its interpretation have introduced bias?** Low risk: "yes" for all signalling questions High risk: "no" or "unclear" for at least one signalling question	**Could the patient flow have introduced bias?** Low risk: "yes" for all signalling questions High risk: "no" or "unclear" for at least one signalling question.
Concerns regarding applicability	**Are there concerns that the included participants do not match the review question?** Low concern: the participants included in the review are those on which the index tests are used in clinical practice (diagnostic work up after positive diagnosis of CRC), and match the criteria given under "Participants" High concern: the participants included in the review differ from the participants in whom the tests are used in clinical	**Are there concerns that the index test, its conduct, or interpretation differ from the review question?** Low concern: the index test(s), its conduct or its interpretation does not differ from the way it is used in clinical practice, and matches the criteria given under "Index test(s)" High concern: the index test(s), its conduct or its interpretation differs from the way it is used in clini-	**Are there concerns that the target condition as defined by the reference standard does not match the review question?** Low concern: the definition of the target condition as defined by the reference standard does match the question (i.e. patients diag-	

(Continued)

	practice, and those who don't match the criteria given under "Participants"	cal practice, and does not match the criteria given under "Index test(s)"	High concern: the definition of the target condition as defined by the reference standard does not match the question (i.e. assessment of test accuracy in detecting liver metastasis originating from tumours other than CRC)

WHAT'S NEW

Date	Event	Description
2 October 2019	New citation required and major changes	We have rewritten the protocol: we made changes to the definition of the clinical pathway, the role of the index tests, and positivity criteria. We described better the reference standard, improved the search strategies, and made changes to the assessment of methodological quality, statistical analysis, sources of heterogeneity, sensitivity analysis, and assessment of reporting bias.

HISTORY

Protocol first published: Issue 10, 2016

CONTRIBUTIONS OF AUTHORS

Martin Lund: content expertise, review expertise, clinical expertise, proposal and writing of the protocol
Tin Nadarevic: content expertise, review expertise, clinical expertise, writing of the protocol
Thomas A Bjerre: clinical expertise
Henning Grønbæk: clinical expertise
Frank V Mortensen: clinical expertise
Per Kragh Andersen: statistical expertise, review expertise
All authors approved the current protocol.

DECLARATIONS OF INTEREST

Martin Lund: none known
Tin Nadarevic: none known
Thomas A Bjerre: none known
Henning Grønbæk has received research grants from Novartis, Ipsen, Abbie, and Intercept, and is the principal investigator for studies sponsored by Ipsen, Novartis, and Intercept. However, none of the declared conflicts is relevant to this review.
Frank V Mortensen: none known
Per Kragh Andersen: none known

NOTES

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